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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,330	06/21/2005	Nathan Bryan Mantlo	X-15710	8686

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	**PAPER NUMBER**
1626	

NOTIFICATION DATE	DELIVERY MODE
04/15/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/540,330	MANTLO ET AL.	
	Examiner	Art Unit	
	JASON M. NOLAN	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,7-10,12-22,24-27,29,30,32-35,37-44,46-48,50,57 and 58* is/are pending in the application.

4a) Of the above claim(s) *37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,46-48 and 50* is/are rejected.

7)☒ Claim(s) *7-10,12-22,24-27,29,30,32-35,37-44,57 and 58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicants Amendment – After Non-Final Rejection, filed **01/28/2008**. **Claims 4, 7-10, 12-22, 24-27, 29, 30, 32-35, 37-44, 46-48, 50, 57, & 58** are pending in the instant application; of which, **Claims 4, 7, 10, 12, 16, 21, 22, 24, 29, 30, 32-35, 39, 42-44, 46-48, 50, 57, & 58** are currently amended, **Claims 37 & 38** are withdrawn, and **Claims 1-3, 5, 6, 11, 23, 28, 31, 36, 45, 49, 51-56, 59, & 60** are canceled.

Response to Amendment

Applicant's amendments with respect to **Claims 4, 7, 10, 12, 16, 21, 22, 24, 29, 30, 32-35, 39, 42-44, 46-48, 50, 57, & 58** have been fully considered and are entered. The 102 & 103 prior art rejections of **Claims 4, 8, 11-18, 20-22, 24-26, 30, 32-34, 44, 46-48, 50, 52, 56, & 57** over Beswick *et al.* (US 7,091,237) are withdrawn per amendment. The 112-enablement rejection over Claims 51 & 53-55 is withdrawn per amendment. The objections to **Claims 4, 5, 10, 12, 21, 22, 30, 32, 36, 37, 39, 56, & 57** are withdrawn per amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of the formula I, including pharmaceutically acceptable salts thereof; the specification is not enabled for *solvates and hydrates* thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Nature of the Invention

The nature of the invention is the compounds of formula I, including all pharmaceutically acceptable salts, solvates, and hydrates thereof.

The state of the prior art and the predictability or lack thereof in the art

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance

characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization, (Morissette *et al.* Advanced Drug Delivery Reviews **2004**, *56*, 275-300).

Amount of direction/guidance & presence or absence of working examples

The direction or guidance present in the instant specification for the preparation of the compounds of formula I is found on pages 39-91 of the specification. However, there are no working examples present in the disclosure for making solvates of formula I. Therefore, one of skill in the art would be required to identify the correct solvent system and solvate technique for each compound/solvate.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include any solvates of formula I.

The quantity of experimentation necessary

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any solvates of a compound of formula I as instantly claimed. The science of producing solvates is unpredictable, such that, without guidance or working examples for in the specification, the claims lack enablement. This rejection can be overcome by deletion of the words "solvates and hydrates" from the **Claim 4**.

Claim Rejections - 35 USC § 112, 1st Paragraph

Claims 46, 47, & 50 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compounds and compositions of formula I and a method of *treating* diabetes, metabolic syndrome, and atherosclerosis, does not reasonably provide enablement for preventing said disorders, (the definition of "treating" on page 27 of the specification includes "preventing"). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention is compounds and compositions of Formula I and methods of using these compounds as pharmaceutical agents.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. *In the instant case*, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a *treatment* for diabetes, metabolic syndrome, and atherosclerosis, but it does not mean that the same group of compounds and compositions may prevent diabetes, metabolic syndrome, and atherosclerosis.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for the *preventing* of diabetes, metabolic syndrome, and atherosclerosis as indicated. The direction or guidance present in Applicants' Specification for a method of using the compounds and compositions of Formula I to *treat* clinical conditions of diabetes, metabolic syndrome, and atherosclerosis is found on pages 92-107 of the specification.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 46, 47, & 50 are drawn to a method of treating diabetes, metabolic syndrome, and atherosclerosis. The specification expands the scope of the term "treating" to include prevention. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. Deleting the word "treating" in **Claims 46, 47, & 50** can overcome this rejection. Examiner suggests changing the term to "A method of mitigating the

progression of the symptoms associated with diabetes," or something that has support from p. 27: ll. 17-20.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "modulating" in **Claim 48** is a relative term which renders the claim indefinite. The term "modulating" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the instant application, does modulate mean that the compounds inhibit PPAR or activate PPAR? Does it mean that the compounds act as agonists or antagonists? A more descriptive term is needed; or Examiner suggests cancelling the claim.

Claim Objections

Claim 4 is objected to because of the following informalities: the same compound (species) is listed twice at the end of the claim. Appropriate correction is required.

Claim 37 is objected to because of the following informalities: the claim depends from canceled subject matter and should be canceled. Further, if amended to depend from **Claim 4**, it would be a duplicate of **Claim 12**. Appropriate correction is required.

Claims 7-10, 12-22, 24-27, 29, 30, 32-35, 38-44, 57, & 58 are objected to as being dependent upon a rejected base **Claim 1**, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

The compounds of formula I are free of the prior art; therefore, when **Claim 4** is found allowable, withdrawn **Claim 38** may be rejoined.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is Jason.Nolan@uspto.gov. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jason M. Nolan, Ph.D./
Examiner, Art Unit 1626

/Rebecca L Anderson/
Primary Examiner, Art Unit 1626